



Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients

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BACKGROUND: At major combat hospitals, the military is able to provide blood products to include apheresis platelets (aPLT), but also has extensive experience using fresh whole blood (FWB). In massively transfused trauma patients, we compared outcomes of patients receiving FWB to those receiving aPLT.

STUDY DESIGN AND METHODS: This study was a retrospective review of casualties at the military hospital in Baghdad, Iraq, between January 2004 and December 2006. Patients requiring massive transfusion (≥ 10 units in 24 hr) were divided into two groups: those receiving FWB ($n = 85$) or aPLT ($n = 284$) during their resuscitation. Admission characteristics, resuscitation, and survival were compared between groups. Multivariate regression analyses were performed comparing survival of patients at 24 hours and at 30 days. Secondary outcomes including adverse events and causes of death were analyzed.

RESULTS: Unadjusted survival between groups receiving aPLT and FWB was similar at 24 hours (84% vs. 81%, respectively; $p = 0.52$) and at 30 days (60% versus 57%, respectively; $p = 0.72$). Multivariate regression failed to identify differences in survival between patients receiving PLT transfusions either as FWB or as aPLT at 24 hours or at 30 days.

CONCLUSIONS: Survival for massively transfused trauma patients receiving FWB appears to be similar to patients resuscitated with aPLT. Prospective trials will be necessary before consideration of FWB in the routine management of civilian trauma. However, in austere environments where standard blood products are unavailable, FWB is a feasible alternative.

Trauma is a leading cause of death in adults worldwide¹ and a large proportion of such trauma deaths occur within the first 6 to 24 hours after injury secondary to uncontrolled hemorrhage.²⁻⁶ In addition to rapid surgical control of bleeding, resuscitation with blood products is an

ABBREVIATIONS: AIS(s) = Abbreviated Injury Scale(s); aPLT = apheresis platelets; ARDS = adult respiratory distress syndrome; CSH(s) = Combat Support Hospital(s); FWB = fresh whole blood; GCS = Glasgow Coma Score; INR = international normalized ratio; ISS(s) = Injury Severity Score(s); JTTR = Joint Theater Trauma Registry; MT = massive transfusion; RTS(s) = revised trauma score(s); SBP = systolic blood pressure; TRISS(s) = Trauma-Injury Severity Score(s).

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important aspect of care for trauma patients.^{7,8} Massive transfusion (MT; commonly defined as 10 or more units of blood within 24 hours)⁹ occurs in approximately 1% to 3% of civilian trauma admissions^{4,10} and this specific subset of patients suffers a high mortality.^{11,12} MT patients require extensive blood banking support to provide additional blood products such as plasma or platelets (PLTs) intended to prevent or manage coagulopathy.^{11,13-27}

The military is frequently faced with the need to treat casualties in austere environments where component products such as plasma or PLTs are unavailable. In such circumstances, the US military has acquired extensive experience collecting and transfusing fresh whole blood (FWB).^{28,29} A recent analysis of combat-related trauma patients receiving 1 or more units of blood reported that FWB was associated with improved survival when compared to component therapy.³⁰ Based on such analysis, some military trauma providers have begun to consider the routine use of FWB even when other components are available. The US Army's Combat Support Hospital (CSH) in Baghdad, Iraq, has had stored red blood cells (RBCs), fresh-frozen plasma (FFP), cryoprecipitate, and FWB since the beginning of Operation Iraqi Freedom in 2003. In November 2004, the CSH began collecting apheresis platelets (aPLT) on site. Because both aPLT and FWB were available at a single institution with an extraordinary volume of casualties, we sought to determine if FWB was associated with improved survival compared to aPLT in MT casualties receiving PLT-containing components.

MATERIALS AND METHODS

Patients

This study was conducted under a protocol reviewed and approved by the Department of Clinical Investigation at Brooke Army Medical Center in San Antonio, Texas, and in accordance with the approved protocol. We performed a retrospective review of all trauma patients admitted to the CSH located at Ibn Sina Hospital in Baghdad, Iraq, between January 2004 and December 2006. Patients who received a MT were identified. Patients receiving neither FWB nor aPLT, as well as patients receiving *both* FWB and aPLT within the first 24 hours from admission, were excluded from the analysis. Patients who were treated initially at forward surgical units or local hospitals before transfer to Ibn Sina Hospital or who received their MT on a day other than on admission (e.g., after the first 24 hr as with an excision or grafting of burns or gastrointestinal bleed) were also excluded from analysis. Finally, because FWB requires a minimum of 30 minutes to collect and process before transfusion, patients expiring in less than 30 minutes from admission were excluded from the analysis. Two groups of patients were defined and evaluated: 1) patients receiving aPLT but no FWB (aPLT group) and 2)

patients receiving FWB but no aPLT (FWB group). The primary outcomes evaluated were survival at 24 hours and at 30 days.

Data sources

Theater transfusion records maintained within the Department of Defense Armed Services Blood Program Office database in Falls Church, Virginia, were used to identify MT patients and transfused blood products. The Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute for Surgical Research at Ft Sam Houston in San Antonio, Texas, was used to determine baseline patient demographics and to determine outcomes for patients. Individual patient chart review was conducted directly from paper charts or from electronically scanned inpatient records maintained by the military's Patient Administration Systems and Biostatistics Activity. Abbreviated Injury Scales (AISs) and Injury Severity Scores (ISSs) were centrally scored and calculated by trained research nurses and staff using ISS-98 after patient discharge.³¹ Revised trauma scores (RTSs), Shock Index, and Trauma-Injury Severity Scores (TRISs) were calculated using standard formulae.³²⁻³⁴

US soldiers were tracked for survival as they reached higher echelons of care. For US military casualties discharged from the hospital before 30 days, outpatient visits were noted using the Web-based Joint Patient Tracking Application, which provides near real-time information on location and status of injured soldiers. Mortality and dates of death were cross-referenced with Social Security Death Index records and listing of casualties provided on the online website Iraq Coalition Casualty Count (<http://www.icasualties.org>). Iraqi casualties, Coalition troops, or contractors who were discharged before 30 days were generally lost to follow-up unless they were subsequently seen at the hospital as outpatients or were readmitted to the hospital or death was reported. Secondary outcomes included clinically identified adult respiratory distress syndrome (ARDS), multiorgan failure syndrome, infection, and embolic events (venous or arterial) identified from the JTTR, available inpatient records, and discharge International Classification of Diseases, 9th Revision, codes. Secondary outcomes also included causes of death due to exsanguination, multisystem organ failure (in patients surviving >24 hr), and sepsis.

Blood components

A common MT protocol was in place at the hospital throughout the study period and has been previously presented.²⁹ Stored blood components (RBCs, FFP, and cryoprecipitate) were obtained almost exclusively from the United States via the Armed Services Blood Program. Post-collection leukoreduction was not uniformly performed

on stored RBC units shipped from the United States. The mean storage age of RBCs at arrival to the CSH from the United States was 27 days, and age at transfusion was 33 days.³⁵ FWB (collected and stored at 22°C for no longer than 24 hr) was donated by questionnaire screened healthy volunteers no more frequently than every 8 weeks as previously described.²⁹ FWB units were nonleukoreduced and the vast majority were transfused within 8 hours of collection.³⁵

Starting in November 2004, aPLT were collected by certified apheresis technologists or technicians and performed strictly following AABB and US Food and Drug Administration guidelines using a mobile collection system (MCS+ 9000, Haemonetics, Braintree, MA). Pedigree donors were used for collections and pheresed no more frequently than every 2 weeks. The number of passes during collection was determined by apheresis machine algorithm (namely using the donor's weight, sex, and predonation PLT count) to get an appropriate yield of more than 3.0×10^{11} thrombocytes (typically six passes, but ranging from five to nine passes). Standard quality control or characterization was performed (PLT count, yield, volume, leukoreduction of the product, and pH). Bacterial cultures were obtained, and if cultures turned positive, the unit was removed from the inventory and destroyed. aPLT products were held for 24 hours before release for transfusion and were stored for up to 5 days at 20 to 24°C.

After aPLT became available at the combat hospital, the use of FWB markedly declined, and when it was used, it was used in combination with standard components, which included aPLT ($n = 51$). Cell savers for reinfusion of shed blood were not used. Initial resuscitation was typically provided with four units of group O blood with 2 units of AB thawed plasma provided in a cooler. Both aPLT and FWB were specifically issued from the blood bank at room temperature and not included in coolers holding other blood products.

Blood product usage and timing of administration were identified from the chart and compared against the JTTR and Armed Services Blood Program Office Blood Bank transfusion record. Discrepancies were reconciled by comparing the times recorded on blood transfusion slips, anesthesia records, intensive care unit records, operative reports, and discharge summaries. Most discrepancies occurred in the context of missing or incomplete blood transfusion slips, double counting of carbon copies of blood transfusion slips, incorrect documentation of blood products (e.g., AB+ FFP recorded as stored RBCs), or failure to attribute emergency release blood products to the specific recipient by the blood bank. Approximately 11% of records had significant discrepancies requiring reconciliation. Crystalloids and colloids administered in the first 24 hours were incompletely documented in many patients. Because of the concern

regarding the quality of these data, fluids were specifically not reported or analyzed.

Statistical analysis

Baseline characteristics, blood product transfusion, recombinant Factor VIIa (rFVIIa) usage, and outcomes were compared between patient groups. [Correction added after online publication: 26-Aug-2010. Factor Ila changed to Factor VIIa.] The total number of RBC units was calculated via the sum of blood units given within the first 24 hours after admission (Total RBC units = Stored RBCs + FWB). Accounting for the amount of plasma contained within FWB and aPLT units (each containing the equivalent of 1 unit of plasma), the total number of "plasma units" was calculated as (FFP + aPLT + FWB) and a "plasma ratio" was calculated as $[(\text{FFP} + \text{aPLT} + \text{FWB}) / (\text{RBC} + \text{FWB})] \times 100$.³⁶ Data were evaluated for normality using Kolmogorov-Smirnov, Shapiro-Wilk, and normality plots. *t* test with Levene's test for equal variances comparison was used to compare parametric data. Mann-Whitney *U* test was used to compare nonparametric data. Pearson chi-square and Fisher's exact tests, as appropriate, were used to compare dichotomous variables. Continuous data are presented as median (range) for nonparametric data or mean (standard deviation) for parametric data. There was no correction of significance to account for multiple comparisons and significance was set at a *p* value of 0.05 or less.

Kaplan-Meier log rank was used to compare unadjusted survival at 24 hours and at 30 days. Univariate regression was used to examine admission and treatment variables associated with mortality. To adjust for confounding affects on survival among the different recorded factors, multivariate analysis was performed using variables with a *p* value of less than 0.2 on univariate analysis. To limit multicollinearity, we avoided variables subsumed within composite measures (e.g., RTS was used in lieu of systolic blood pressure [SBP], respiratory rate, and Glasgow Coma Score [GCS]) and avoided using multiple variables with similar determinants for calculation (e.g., both RTS and Shock Index use SBP). A dichotomous variable representing the FWB versus the aPLT group comparison was created and forced into the models. Multivariate regression models were performed using block entry (no forward or backward selection of variables) and there were more than 20 subjects per variable included in the models. Multivariate logistic regression was used to examine 24-hour mortality and the Cox proportional hazards model was used to examine 30-day mortality. To assess the robustness of the regression, we performed multiple sensitivity analyses without the FWB versus aPLT group dichotomous variable, examining only US personnel, excluding severe head injuries (AIS Head 4 or 5), using only variables available upon admission, using the primary vital signs (SBP, heart rate, GCS), and multiple

different composite measures of severity of injury including Shock Index, ISS, RTS, and TRISS. Statistical analysis was performed with computer software (SPSS 15.0, SPSS, Inc., Chicago, IL).

RESULTS

Over the 36-month period between January 2004 and December 2006, the CSH received 8618 patients with traumatic injuries, of which 2024 (23%) were transfused and 694 (8.1%) received 10 or more units of blood within 24 hours at the hospital. (Fig. 1) Upon review of inpatient records, 325 patients were excluded from the analysis: 198 received neither FWB nor aPLT, 51 received both FWB and aPLT, 57 were treated at forward surgical teams or local hospitals before admission, 18 did not receive their MT within the first 24 hours of admission, and only one patient expired in less than 30 minutes of admission (from the aPLT group). An exploratory look at the data extending out to 60 minutes revealed that an additional patient in the aPLT group died at 46 minutes, and one patient in the FWB group died right at 60 minutes. The small number of early deaths was likely because of the time it takes for a patient to receive a MT, so most of the early deaths were avoided by the inclusion criteria of 10 or more units in 24 hours.

Of the remaining 369 patients, 284 patients received aPLT, and 85 received FWB. The difference in numbers between the two groups is explained in part by the fact that nearly all patients in the FWB group (80/85, 94%) were treated over a 12-month period between January 2004 and December 2004 and all patients in the aPLT group were treated over a 26-month period between November 2004 and December 2006.

Admission characteristics of the patients

The two groups were similar (Table 1) on the basis of age, sex, and mechanism of injury with both groups being primarily young adult males with penetrating injuries. US personnel represented 151 of 369 (41%) of MT casualties, although it represented a larger proportion of patients receiving FWB compared to non-US casualties (US FWB recipients 57.6% vs. non-US 42.4%; $p < 0.001$).

The FWB group had a higher ISSs and lower TRISSs (higher ISS denotes worse injury, and lower TRISS denotes lower predicted survival). Admission temperature was lower in the FWB group than in the aPLT group, although this difference did not appear to be clinically meaningful. The FWB group had more profound acidosis on admission reflected by a lower pH and larger base deficit. The FWB

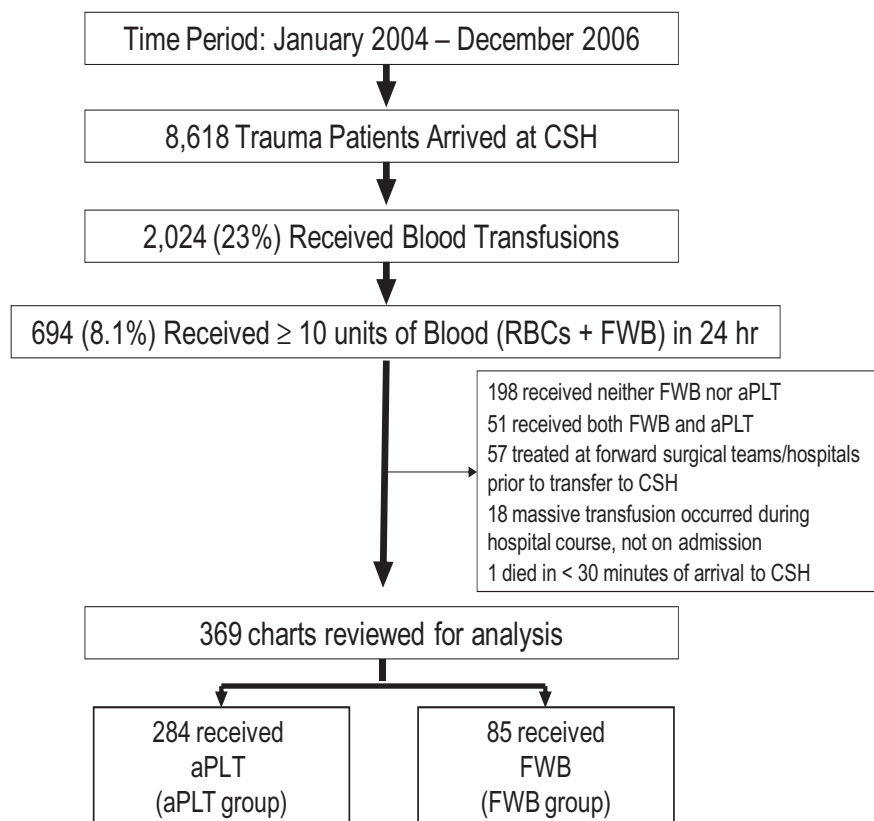


Fig. 1. Study scheme.

TABLE 1. Admission characteristics of massively transfused patients by component group*

| Characteristics | aPLT (n = 284) | FWB (n = 85) | p value† |
|------------------------------------|------------------|------------------|----------|
| Age (years) | 27.4 (±7.2) | 27.6 (±7.6) | 0.85 |
| Sex (male) | 96.8 | 96.5 | 0.87 |
| US nationality | 102/284 (35.9%) | 49/85 (57.6%) | <0.001 |
| Mechanism of injury | | | |
| Penetrating | 93.3 | 91.7 | 0.61 |
| Blunt | 6.7 | 8.3 | |
| Concomitant burn | 1.1 | 0.0 | 1.00 |
| Trauma scores | | | |
| ISS | 21.5 (9-75) | 26 (9-59) | 0.05 |
| Head/neck | 0 (0-5) | 0 (0-5) | 0.10 |
| Face | 0 (0-3) | 0 (0-3) | 0.36 |
| Thorax | 0 (0-6) | 0 (0-6) | 0.87 |
| Abdomen | 0.5 (0-5) | 2 (0-5) | 0.27 |
| Extremity | 3 (0-5) | 3 (0-5) | 0.18 |
| External | 1 (0-5) | 0 (0-2) | 0.15 |
| RTS | 7.11 (0-7.84) | 6.82 (0-7.84) | 0.09 |
| TRISS | 0.84 (±0.24) | 0.74 (±0.32) | 0.02 |
| Shock Index | 1.28 (±0.54) | 1.27 (±0.52) | 0.93 |
| Admission vitals | | | |
| Heart rate (beats/min) | 118 (±26) | 111 (±28) | 0.09 |
| SBP (mmHg) | 101 (±33) | 97 (±35) | 0.17 |
| Temperature (°C) | 36.3 (±1.2) | 35.6 (±1.4) | <0.001 |
| GCS | 12.2 (±4.1) | 11.3 (±4.9) | 0.28 |
| Admission labs | | | |
| pH | 7.24 (6.67-7.52) | 7.19 (6.57-7.44) | 0.02 |
| Base deficit (mEq/L) | 8 (0-30) | 10 (0-30) | 0.04 |
| Hb (g/dL) | 11.1 (±2.5) | 10.6 (±2.8) | 0.09 |
| PLT count (1 × 10 ⁹ /L) | 260 (±102) | 229 (±105) | 0.03 |
| INR | 1.4 (0.5-8.0) | 1.5 (0.7-6.3) | 0.27 |

* Data are expressed as median (range), mean (±SD), or percent.

† Parametric data compared using t test, nonparametric data compared using Mann-Whitney U, and dichotomous variables compared using Pearson's chi-square.

group also had a lower admission PLT count. There were no differences between groups in RTS, Shock Index, AIS by body region, admission heart rate, SBP, GCS, hemoglobin (Hb), or international normalized ratio (INR).

Resuscitation products

Equivalent "total" RBC units were administered to both groups (Table 2). As would be expected based on this, fewer stored RBC units were transfused to the FWB group (Table 2). The median time to FWB transfusion was 3.4 hours (interquartile range, 2.0-5.9) and the median time to aPLT transfusion was 2.5 hours (interquartile range, 1.4-4.4; $p = 0.06$). The aPLT group received more FFP units than the FWB group. This relationship remained true for plasma ratios as well, even after accounting for plasma contained within aPLT and FWB units. More cryoprecipitate units were transfused to the aPLT group than the FWB group. Finally, more patients in the aPLT group received rFVIIa than those in the FWB group, although when administered, the dose of rFVIIa was similar between groups.

Outcomes

Survival at 24 hours was known for all patients and there was no difference in unadjusted survival between groups

at this time point (aPLT 239/284 [84%] vs. FWB 69/85 [81%]; chi-square $p = 0.52$). Both groups had patients who were lost to follow-up. The aPLT group had 107 of 284 (37.6%) patients lost to follow-up after a median of 4.3 days (interquartile range, 2.2-7.4 days) compared to 17 of 85 (20%) from the FWB group after a median of 6.7 days (interquartile range, 3.8-10.1 days; $p = 0.04$). Of patients with known outcomes at 30 days, there were no differences in unadjusted survival (106/177 [60%] vs. 39/68 [57%], respectively; chi-square $p = 0.72$). Unadjusted 30-day Kaplan-Meier log rank analysis (Fig. 2) similarly showed no difference in survival.

A higher incidence of ARDS (Table 3) was noted in the FWB group (ARDS aPLT 7.4% vs. FWB 18.8%; $p = 0.002$). This association remained true even after adjusting for injury severity ($p = 0.003$, data not shown). Given that US casualties represented a larger proportion of patients receiving FWB and were all followed out to 30 days (potential for ascertainment bias), a subgroup of only US casualties was evaluated. In this subset of US casualties, FWB was still associated with a

higher incidence of ARDS (ARDS in US only aPLT 9.8% vs. FWB 22.4%; $p = 0.045$). There were no differences between groups for development of multiorgan failure, infection, or venous or arterial embolic events. A chi-square comparing embolic events to rFVIIa use was not significant ($p = 0.24$). A logistic regression analysis using embolic events as the dependent variable with rFVIIa use and FWB versus aPLT group as covariates similarly showed no significant association with rFVIIa ($p = 0.26$) or with the FWB versus aPLT group ($p = 0.76$). There were no differences in unadjusted death due to exsanguination, multisystem organ failure, or sepsis. Similar adverse outcomes results to the larger data set were noted in a subset of patients without severe head injury (AIS Head <4; data not shown).

Univariate regression analysis of variables was performed examining associations with mortality (Table 4). To adjust for confounding affects on survival among the different recorded factors, multivariate analysis was performed using variables with p values of less than 0.2 on univariate analysis. A dichotomous variable representing the FWB versus the aPLT group comparison was created and forced into the models. Multivariate analyses for mortality at 24 hours and 30 days are shown in Table 5. While the odds ratio (OR) trended in favor for FWB, there was no difference between groups for mortality at 24 hours

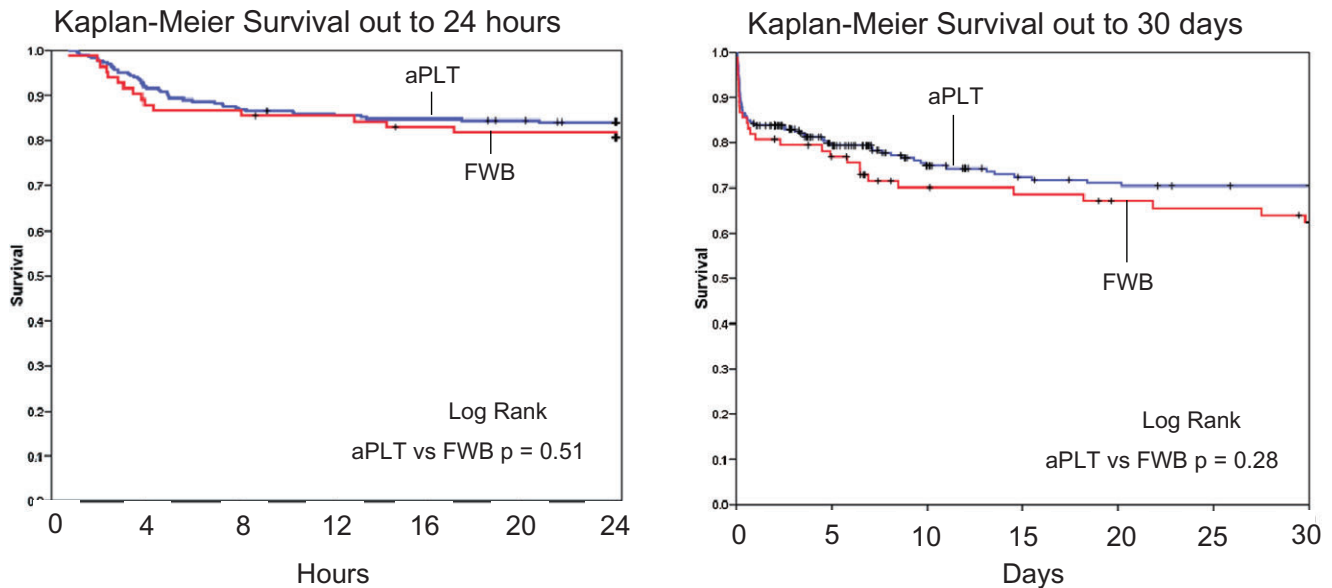


Fig. 2. Unadjusted Kaplan-Meier survival curves comparing FWB to aPLT groups.

TABLE 2. Resuscitation products massively transfused patients in the first 24 hours by component group*

| Resuscitation product | aPLT (n = 284) | FWB (n = 85) | p value† |
|---|----------------|----------------|----------|
| Transfusion products | | | |
| Total RBC units‡ | 19 (10-58) | 19 (10-52) | 0.68 |
| Stored RBC units | 19 (10-58) | 15 (4-42) | <0.001 |
| FWB units | 0 (0-0) | 5 (1-21) | NA |
| aPLT units | 2 (1-9) | 0 (0-0) | NA |
| FFP units | 12 (2-42) | 8 (0-28) | <0.001 |
| Plasma ratio (%)§ | 80 (±25) | 68 (±23) | <0.001 |
| Cryoprecipitate units | 10 (0-52) | 0 (0-29) | <0.001 |
| rFVIIa | | | |
| Given—number of patients/total number of patients (%) | 196/282 (70) | 44/80 (55) | 0.02 |
| Dose (mg) when given | 7.2 (2.4-36.0) | 9.0 (2.4-21.6) | 0.21 |

* Data are expressed as median (range), mean (±SD), or percent, unless otherwise specified.

† Compared using Mann-Whitney U and dichotomous variables compared using Pearson's chi-square.

‡ Total blood units = Stored RBC + FWB units.

§ Plasma ratio = (Plasma + FWB + aPLT)/Total blood units × 100.

TABLE 3. Adverse events and cause of death of massively transfused patients by component group*

| Etiology | aPLT (n = 284) | FWB (n = 85) | p value† |
|-----------------------------|----------------|--------------|----------|
| Adverse events | | | |
| ARDS | 21/284 (7.4) | 16/85 (18.8) | 0.002 |
| Multiorgan failure syndrome | 18/239 (7.5) | 9/69 (13.0) | 0.15 |
| Infection | 71/284 (25.0) | 22/85 (25.9) | 0.87 |
| Embolic event | 37/284 (13.0) | 9/85 (10.6) | 0.55 |
| Cause of death | | | |
| Exsanguination | 32/284 (11.3) | 13/85 (15.3) | 0.32 |
| Multiorgan failure syndrome | 16/239 (6.7) | 5/69 (7.2) | 0.87 |
| Sepsis | 11/284 (3.9) | 5/85 (5.9) | 0.43 |

* Data are expressed as number (%) and compared using Fisher's exact unless otherwise indicated.

† Compared using chi-square or Fisher's exact as indicated.

($p = 0.06$). At 24 hours, higher numbers of blood units were independently associated with increased mortality, whereas higher TRISS and plasma ratio were independently associated with decreased mortality. This model had a $R^2 = 0.56$ and area under the receiver operating characteristics curve value of 0.93. At 30 days, there was no difference between groups for mortality ($p = 0.28$). A higher admission INR was independently associated with increased 30-day mortality. US nationality, higher TRISS, and plasma ratio were associated with decreased 30-day mortality. Both regressions were analyzed without the forced aPLT versus FWB variable, and there were no changes in the relationship of the remaining variables except that at 24 hours, US nationality was associated with improved survival ($p = 0.02$). Multiple sensitivity analyses were performed as described under Materials and Methods. Despite multiple varied analyses, there was no influence on the finding of equivalence between aPLT and FWB groups for mortality at 24 hours or at 30 days (data not shown).

DISCUSSION

This is the largest comparative analysis of FWB and aPLT in MT casualties

reported to date. The trend toward improved survival at 24 hours for patients receiving FWB is notable, although this trend did not extend out to 30 days. Patients receiving FWB had a higher incidence of ARDS, which may have led to an increase in late deaths accounting in part for the equivalence in survival between groups at 30 days. It is notable that both the aPLT and the FWB groups received similar numbers of total RBC units. Apart from this indirect comparison of hemostatic efficacy, the equivalent survival outcome also suggests that the fresh RBCs provided by FWB did not substantially improve survival compared to uniform use of older stored RBCs, at least at the

volumes transfused. While these findings do not support the routine use of FWB in MT trauma patients when all components are available, they do show that when stored blood components such as PLTs are unavailable, FWB is a feasible alternative.

Since the advent of fractionated blood components, whole blood for specific indications such as MT has remained a subject of interest. Advocates of FWB use have suggested that in situations of extensive blood loss, whole blood counters the dilutional effects of additive solutions,³⁷ limits donor exposures,³⁸ simplifies the logistics of transfusing multiple products to patients,³⁹ and reduces the risk of hypothermia because of storage at room temperature. There are other theoretical reasons FWB might be superior to stored blood products: fresh RBCs may not confer the risk of increased morbidity and mortality that has been associated with RBC units stored for more than 14 days;^{35,40,41} plasma from FWB is replete with labile factors (FV and FVIII), which rapidly degrade in thawed plasma;^{42,43} and FWB has been specifically advocated for use to treat microvascular bleeding refractory to standard blood components.⁴⁴⁻⁴⁶ Regardless of such considerations, for the military the most germane reason for use of FWB is its availability even in the most austere conditions where supply of conventional blood components is often limited.

In the civilian world, however, there are significant practical limitations to the availability of FWB: rapid mobilization of donors for collection is resource-intensive and faces significant logistical obstacles, required safety testing is time-consuming, and FWB has a very short shelf-life (up to 8 hours stored at room temperature) although there are data to suggest that it may be stored up to 72 hours.⁴⁷ Fractionation of FWB into multiple different blood components enables optimal storage of each component, which can then be available to multiple different patients. Finally, there are valid safety concerns regarding the use of fresh blood, which has been associated with

TABLE 4. Univariate relationship of variables to mortality for massively transfused patients

| Variable | Mortality hazard ratio (95% CI) | p value* |
|---------------------------------|---------------------------------|----------|
| Demographics | | |
| US nationality | 0.56 (0.47-0.85) | 0.01 |
| Age | 0.99 (0.97-1.02) | 0.65 |
| Male sex | 1.65 (0.67-4.07) | 0.27 |
| Penetrating mechanism of injury | 0.99 (0.46-2.14) | 0.98 |
| TRISS | 0.73 (0.68-0.78) | <0.001 |
| Vitals—laboratory tests | | |
| Temperature (°C) | 0.83 (0.71-0.98) | 0.03 |
| Heart rate (beats/min) | 1.00 (0.99-1.01) | 0.42 |
| Hb (g/dL) | 0.96 (0.88-1.03) | 0.26 |
| PLT count ($1 \times 10^9/L$) | 1.00 (0.999-1.001) | 0.18 |
| INR | 1.33 (1.17-1.61) | <0.001 |
| Base deficit (mEq/L) | 1.06 (1.03-1.08) | <0.001 |
| Resuscitation products | | |
| Total RBC units† | 1.03 (1.01-1.05) | <0.001 |
| Plasma ratio (%)‡ | 0.98 (0.97-0.99) | 0.07 |
| Cryoprecipitate units | 0.99 (0.97-1.01) | 0.35 |
| rFVIIa usage | 1.35 (0.86-2.10) | 0.19 |

* Hazard ratio for mortality determined using Cox proportional hazards regression.
† Total RBC units = Stored RBCs + FWB units.
‡ Plasma ratio (%) = (Plasma + FWB + aPLT)/Total blood units \times 100.

TABLE 5. Multivariate regression analyses of massively transfused patients at 24 hours and at 30 days

| Variable | Logistic regression for mortality at 24 hr* | | Cox regression for mortality at 30 days | |
|---------------------------------|---|---------|---|---------|
| | OR (95% CI) | p value | Hazard ratio (95% CI) | p value |
| aPLT group† | 3.38 (0.96-11.87) | 0.06 | 1.38 (0.77-2.47) | 0.28 |
| US nationality | 0.35 (0.12-1.02) | 0.054 | 0.33 (0.18-0.59) | <0.001 |
| TRISS | 0.57 (0.44-0.74) | <0.001 | 0.71 (0.64-0.79) | <0.001 |
| Temperature (°C) | 0.69 (0.48-1.01) | 0.055 | 1.00 (0.84-1.21) | 0.96 |
| PLT count ($1 \times 10^9/L$) | 1.00 (0.99-1.01) | 0.17 | 1.00 (0.99-1.01) | 0.13 |
| INR | 1.45 (0.97-2.16) | 0.07 | 1.21 (1.01-1.45) | 0.04 |
| Base deficit (mEq/L) | 1.05 (0.98-1.13) | 0.14 | 1.02 (0.99-1.06) | 0.23 |
| Total RBC units‡ | 1.06 (1.02-1.11) | 0.01 | 1.02 (0.99-1.04) | 0.17 |
| Plasma ratio (%)§ | 0.94 (0.92-0.97) | <0.001 | 0.99 (0.98-0.999) | 0.03 |
| rFVIIa usage | 0.86 (0.29-2.57) | 0.79 | 1.05 (0.61-1.83) | 0.85 |

* Multivariate logistic regression model had Nagelkerke $R^2 = 0.56$; area under the receiver operating characteristics curve, 0.93.

† Comparison to reference FWB group.

‡ Total RBC units = Stored RBCs + FWB units.

§ Plasma ratio (%) = (Plasma + FWB + aPLT)/Total blood units \times 100.

microchimerism and increased risk for transfusion-associated graft-versus-host disease.^{48,49}

As of April 2010, more than 7300 units of FWB have been transfused to combat casualties in Iraq and Afghanistan compared to more than 128,000 units of RBCs.⁵⁰ In 2009, Spinella and coworkers³⁰ retrospectively compared FWB use to component therapy specifically including aPLT in US soldiers ($n = 354$) receiving *one or more* units of blood. Multivariate analysis including ISS, plasma ratio, GCS eye, and base deficit as covariates suggested that FWB was independently associated with improved survival. The data for the Spinella publication were derived from a separate data set and differences between patient populations chosen for analysis may explain the discordant results. A strength of the Spinella publication was that outcomes were known for *all* patients out to 30 days, whereas outcomes for this paper were not known for all patients, which limited the power to detect statistical differences. Spinella examined data from multiple medical facilities in both Iraq and Afghanistan, whereas this paper examined casualties at a single institution in Baghdad. Spinella included patients receiving even a single unit of blood, which may have introduced additional survival bias in favor of FWB. Patients may have died early before they could be adequately resuscitated (as with a MT) and patients receiving FWB had to survive long enough for the FWB to be request, collected, processed, and released for transfusion (compared to the relatively immediate availability of aPLT). This survival bias might have been reduced by excluding very early deaths as we have in this paper, but the Spinella publication did not exclude such patients. Spinella included only US military casualties, so injury patterns may have been different because US personnel are generally protected with body armor. Finally, this paper may be less affected by referral bias as we excluded patients who were treated at forward surgical teams, whereas the Spinella paper included patients treated at these far-forward facilities. Forward surgical teams do not have aPLT available (and require FWB collection if PLTs are needed). Such far-forward facilities with reduced surgical capabilities may have triaged patients with severe injuries differently than the major CSHs that use aPLT.

Randomized data comparing FWB with component therapy in trauma do not yet exist, although prospective data in cardiothoracic surgery are available. Five prospective randomized trials have been conducted: three examined FWB in comparison to component therapy,^{45,51,52} one compared "reconstituted fresh whole blood" (separated at collection, stored up to 2 days, and then reconstituted at infusion) to standard blood components,⁵³ and one study compared autologous FWB reinfusion to standard postoperative management with or without transfusion.⁵⁴ Four of these studies were in infant or pediatric patients, and one was in adult patients. All reported improved

hemostatic function with FWB attributed to fresh functional PLTs, although none showed a survival benefit. Randomized trials would be helpful in determining whether FWB is superior in trauma populations, although this would be extraordinarily difficult to perform given the limited shelf life of FWB. Furthermore, based on this analysis of 369 massively transfused patients showing no difference in survival at 30 days, one would anticipate that a large clinical trial would be needed to provide sufficient power to detect survival differences between FWB and component therapy.

Limitations

There are limitations associated with such a retrospective analysis: 1) Given that aPLT were only available after November 2004, there may have been bias introduced from improvements in care over time based on increased trauma care expertise, changing patterns in resuscitation, and a maturing trauma system; 2) as noted above, outcomes were not known for all patients out to 30 days reducing the power to detect statistical differences; 3) we did not attempt to ascertain or control for periods of limited blood product resources such as during mass casualty situations; 4) survival bias in favor of FWB is inherent as it generally takes at least 30 to 45 minutes after FWB is ordered for it to be collected, processed, and transfused. Rapidly exsanguinating patients may not have survived long enough to receive FWB, but could have survived long enough to receive the more readily available aPLT (generally available from the blood bank within 5-10 minutes of the request). This bias is potentially reflected in a 2.5-hour median time to aPLT transfusion, which was nearly 1 hour earlier than the 3.4-hour median time to FWB transfusion.

Complications of ARDS, multiorgan failure syndrome, infection, and thromboembolic events were based on clinical impressions with supporting laboratory and radiographic studies. Such adverse event data are limited because neither formal criteria nor prospective screening modalities were used to establish diagnoses. For instance, the characterization of ARDS may have been misclassification of pulmonary edema from volume overload during resuscitation. An additional limitation is that we did not report on important secondary outcomes such as ventilator days, intensive care unit days, or hospital length of stay.

The findings of this study are limited to a minority of patients, those receiving a MT in the setting of trauma, and thus care should be taken before extrapolating these results to patients undergoing elective surgery or patients expected to receive fewer than 10 units of blood. The injuries in this patient population were primarily due to penetrating injuries (e.g., high-velocity gunshot wounds and fragmentation injuries) and these findings may not apply

to trauma populations who present primarily with blunt injuries (e.g., motor vehicle accidents and falls). Finally, these data only show associations with survival and do not prove causality for any interventions. As such, these data are hypothesis-generating and cannot be used to make definitive conclusions about the best care for trauma casualties.

In conclusion, survival for massively transfused trauma patients receiving FWB appears to be similar to patients resuscitated with aPLT. The military is often faced with logistical challenges to the supply of blood products far forward and similar conditions can exist for civilians in remote locations with limited evacuation capability or blood banking resources. In such situations, trauma providers might consider emergency plans incorporating the use of FWB. Prospective trials will be necessary to define the actual efficacy of FWB and to explore potential pulmonary toxicity before consideration of FWB in the routine management of civilian trauma.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to the subject matter of this article. PCS, CEW, and JBH have received grant money from the US Army for the conduct of research related to trauma.

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